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Uptake of endoscopic screening for gastroesophageal varices and factors associated with variceal bleeding in patients with chronic hepatitis C infection and cirrhosis, 2005–2016: a national database linkage study

Running title: Endoscopic screening for varices in HCV patients

Scott A. McDonald, smcdonald4@nhs.net, School of Health and Life Sciences, Glasgow Caledonian University and Health Protection Scotland, Glasgow, UK

Stephen T. Barclay, stephenbarclay@nhs.net, Glasgow Royal Infirmary, Glasgow, UK

Sharon J. Hutchinson, sharon.hutchinson2@nhs.net, School of Health and Life Sciences, Glasgow Caledonian University and Health Protection Scotland, Glasgow, UK

Adrian J. Stanley, adrian.stanley@ggc.scot.nhs.uk, Glasgow Royal Infirmary, Glasgow, UK

Andrew Fraser, afraser2@nhs.net, Aberdeen Royal Infirmary, Aberdeen, UK

John F. Dillon, j.f.dillon@dundee.ac.uk, School of Medicine, University of Dundee, Dundee, UK

Hamish A. Innes, hamish.innes@nhs.net, School of Health and Life Sciences, Glasgow Caledonian University and Health Protection Scotland, Glasgow, UK

Erica Peters, erica.peters@ggc.scot.nhs.uk, Queen Elizabeth University Hospital, Glasgow, UK

Nicholas Kennedy, nicholas.kennedy@lanarkshire.scot.nhs.uk, University Hospital Monklands, Lanarkshire, UK

Andrew Bathgate, andy.bathgate@nhslothian.scot.nhs.uk, Royal Infirmary of Edinburgh, Edinburgh, UK

Peter Bramley, peter.bramley@nhs.net, Stirling Royal Infirmary, Stirling, United Kingdom

Judith Morris, judith.morris@nhs.net, Queen Elizabeth University Hospital, Glasgow, UK

David J. Goldberg, david.goldberg2@nhs.net, School of Health and Life Sciences, Glasgow Caledonian University and Health Protection Scotland, Glasgow, UK

Peter C. Hayes, p.hayes@ed.ac.uk, Royal Infirmary of Edinburgh, Edinburgh, UK

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SUMMARY

Background. Primary measures for preventing morbidity and mortality associated with bleeding gastroesophageal varices in cirrhotic patients include endoscopic screening.

Aims. Among cirrhotic hepatitis C virus (HCV) patients attending specialist care in Scotland, to identify factors associated with (i) screening and (ii) a first hospital admission for variceal bleeding.

Methods. The Scottish Hepatitis C Clinical Database was linked to national hospitalisation and deaths records to identify all chronic HCV patients diagnosed with cirrhosis in 2005–2016 (*n*=2741). The adjusted odds of being screened by calendar year period were estimated using logistic regression, and the adjusted hazard ratio (HR) of a first variceal bleed using Cox regression.

Results. 34% was screened within 12 months before/after cirrhosis diagnosis. The proportion screened was stable in 2005–2010 at 42%, declining to 37% in 2011–2013 and 26% in 2014–2016. Odds of screening were decreased for age-groups <40 (OR=0.61, 95% CI:0.48–0.77) and 60+ years (OR=0.67, 95% CI:0.48–0.94), history of antiviral therapy (OR=0.70, 95% CI:0.55–0.89), and cirrhosis diagnosis in 2014–2015, compared with 2008–2010 (OR=0.67, 95% CI:0.52–0.86). Compared with 2008–2010, there was no evidence for an increased/decreased relative risk of a first variceal bleed in any other period, but viral clearance was associated with a lower risk (HR=0.56, 95% CI:0.32-0.97).

Conclusions. Overall screening uptake following cirrhosis diagnosis was low, and the decline into the IFN-free therapy era is of concern. The stable bleeding risk over time may be attributable both to ongoing prevention initiatives and to changing diagnostic procedures creating a patient pool with milder disease in more recent years.

KEYWORDS

Oesophageal and gastric varices; endoscopy; screening; hepatitis C virus; gastrointestinal

haemorrhage

INTRODUCTION

Portal hypertension, as a consequence of progressive liver disease caused by chronic infection with the hepatitis C virus (HCV), can give rise to severe complications such as bleeding gastroesophageal varices. Variceal haemorrhage can be life-threatening, and even if treated carries an estimated mortality risk of 15–20% within six weeks following the first bleed.[1-3]

Screening of cirrhotic patients with HCV infection for varices by endoscopy is an established strategy for identifying patients at-risk for variceal bleeding. Guidelines for screening followed by appropriate pharmacological or other prevention measures have long been available.[4,14] However, there have been very few national-level studies investigating real-world adherence to screening guidelines,[5] or reporting rates of variceal bleeding over time among populations of individuals with chronic HCV infection.

The monitoring of temporal trends in the occurrence of variceal bleeding has perhaps gained in importance with the scaled-up deployment of the new generation of interferon-free (IFN-free) antiviral therapies for chronic HCV infection, increasing the number of treated patients with cirrhosis achieving a sustained virologic response (SVR). In Scotland and elsewhere, these drugs show great promise for reducing the rising HCV-related liver disease burden, including a decreased progression from compensated to decompensated cirrhosis (DC).[6] Nevertheless, vigilance to variceal screening should not be relaxed, as one impact of a scale-up in IFN-free treatment will be an increasing number of HCV patients living with cirrhosis.

UK guidelines recommend endoscopic screening in all patients with cirrhosis,[7] and practice at most Scottish specialist liver clinics is to schedule a first endoscopy once diagnosis of cirrhosis made. Screening recommendations were recently fine-tuned at the most recent Baveno VI consensus conference and published in September 2015[14], with the aim to identify compensated

cirrhosis patients at very low risk for variceal bleeding; such patients could be excluded from endoscopic screening if they had liver stiffness by transient elastography <20 kPa and a platelet count >150,000/mm^3. Given the long-standing availability of guidelines for screening of cirrhotic patients, it is of interest to know if there has been an impact on variceal bleeding rates from endoscopic screening over the last decade. As this question cannot be addressed directly from observational data, we formulated the following study objectives: (i) describe the uptake of endoscopic screening over time amongst HCV-infected cirrhotic patients with no known history of variceal bleeding, and investigate the factors associated with screening uptake in this patient population; (ii) describe the frequency and rates of a first variceal bleeding episode in the same population over the same period, and assess the factors associated with the risk of a first bleed. We anticipated that screening practice may have led to improvements in bleeding rates over our study period. A specific aim under both objectives was to investigate any difference in outcome comparing pre-IFN-free (before 2014) and IFN-free (from 2014 onwards) treatment eras.

METHODS

All analyses

Data sources. The Scottish Hepatitis C Clinical Database is a comprehensive record of all HCV patients attending specialist tertiary care and represents 17 out of 18 specialist clinics across Scotland.[8] This database encodes detailed clinical and epidemiological information on patients attending a specialist clinic for care/management of HCV infection; informed 'opt-out' consent was obtained for use of their data. The HCV Clinical Database was electronically linked to the national deaths registry and the Scottish Morbidity records (SMR01; a database holding all acute inpatient and daycase hospital episodes held by Information Services Division (ISD)) by ISD using probabilistic methods.[9] The resulting linkage was anonymised before analysis.

Study population and setting. The study population consisted of all patients with chronic HCV

infection on the Scottish Hepatitis C Clinical Database diagnosed with cirrhosis between 1 January 2005 and 31 December 2016, with no history of variceal bleeding (according to information held on this database), and who had been diagnosed with cirrhosis no earlier than one year prior to their first attendance at one of Scotland's specialist liver clinics (to ensure continuity of clinical care for potential referral for endoscopy). In our study population, cirrhosis was diagnosed via a combination of biopsy, transient elastography (FibroScan®), abdominal ultrasound, clinical examination, and routine liver function tests. We estimated the annual proportion of all cirrhosis diagnoses that were made using transient elastography by matching the cirrhosis diagnosis date for each patient to dates of diagnostic procedures held in a separate table.

The eligible study population for the descriptive analysis and analysis of bleeding risk (see below) was larger than for the analysis of screening uptake; the former were diagnosed with cirrhosis within the period 2005–2016, which we term the 'entire period' study population, and the latter in 2005–2015 (to allow 12 months for endoscopic screening following diagnosis).

Endoscopic screening was determined via the procedure code fields in SMR01; we assumed the presence of one or more of this procedure code set indicated screening endoscopy. Both non-bleeding and bleeding oesophageal varices episodes were identified via the presence of discharge diagnoses codes (using International Classification of Disease (ICD10); see Supporting Information, Table S1) in the same data source. These codes have been used extensively in previous research by ourselves and others.[10,11] Note that discharge diagnoses are entered for day-cases as well as for inpatient admissions. The record-linkage also provided date of death, required for censoring.

Descriptive analysis. We plotted the number of persons screened and the number of first bleeds

among the 'entire period' study population, by year of event. Rates of first variceal bleed over calendar year period were computed using person-time-methods (i.e., events divided by person-time at risk).

Uptake of variceal screening

Regression analysis. Logistic regression analysis was conducted on the '2005-2015' study population to estimate the association between first endoscopic screening within 12 months prior to or subsequent to date of cirrhosis diagnosis and period of diagnosis (2005-2007, 2008-2010, 2011-2013, 2014-2015; multiple periods allow potential trends to be observed, with 2008-2010 logically selected as reference category), adjusting for a number of covariates. To allow a minimum of 12 months to observe an endoscopic procedure following cirrhosis diagnosis, analysis was restricted to cirrhosis diagnoses made before or on 31 December 2015; hence the total and number of patients per covariate level differ between Tables 1 and 2. Covariates of interest included sex, age-group at diagnosis (<40, 40-49, 50-59, 60+ years), ethnicity (white, non-white), risk group (people who inject drugs [PWID], non-PWID/not known; combined post-hoc on basis of similar estimated coefficients), historical alcohol use (self-reported: >50 units per week, ≤50 units per week/not known), initiation on antiviral treatment at baseline (ie. prior to cirrhosis diagnosis date), the presence of ascites and encephalopathy at baseline (according to information on the Clinical Database), and mode of cirrhosis diagnosis: radiology (which includes ultrasound and FibroScan®), clinical examination, or other/not known (which includes biopsy).

Sensitivity analyses. We also investigated the association between period of cirrhosis diagnosis and variceal screening among three subgroups of the study population: (a) patients likely to have more advanced disease (defined as the presence of ascites at baseline); (b) patients inferred to have been diagnosed with cirrhosis using FibroScan® (i.e., more likely to have early, less advanced cirrhosis); and (c) patients not known to have been diagnosed using FibroScan®. To

address possible increasing use of Baveno VI criteria to exclude very low-risk patients from screening, we additionally investigated – among the subgroup of patients with available platelets counts – the association between period of cirrhosis diagnosis and the odds of endoscopy among patients under and over the platelet count threshold (150k/mm^3 , Baveno VI[14])

First admission for bleeding varices following cirrhosis diagnosis

Regression analysis. Cox proportional-hazards regression analysis was conducted to estimate the adjusted hazard ratio of a first variceal haemorrhage according to calendar year period (2005-2007, 2008-2010, 2011-2013, 2014-2016). Covariates considered were: sex, age-group, ethnicity (white, non-white), risk group (PWID, non-PWID/not known), historical alcohol use (self-reported: >50 units per week, ≤50 units per week/not known), initiation on/outcome of antiviral therapy (never treated, non-SVR, or SVR), first ascites occurrence, first encephalopathy occurrence, and mode of cirrhosis diagnosis (radiology/ultrasound/FibroScan®, clinical examination, or other/not known). Age, antiviral treatment, ascites, and encephalopathy were all specified as time-dependent (also known as time-updated) covariates. Follow-up was defined to begin on the date of cirrhosis diagnosis and to end at the earliest of first bleed, death, or 31 December 2016. The inclusion of covariates in the multifactorial model was determined by a (pre-specified) $P \leq 0.25$ obtained in univariate analysis. The Cox proportional hazards assumption was confirmed graphicallyusing Schoenfeld residuals.

All statistical analyses were conducted in the R statistical programming environment, version 3.0.3.[12]

Estimation of sensitivity of endoscopic procedure codes

To determine the sensitivity of the SMR01 codeset used to define an inpatient/daycase hospital admission for endoscopic screening, we carried out a validation study using data on endoscopic

procedures in the HCV Clinical Database held by a single clinic, Glasgow Royal Infirmary (GRI). Data on the HCV Clinical Database were considered as the gold standard (with GRI taken as a representative sample) and the overlap in individual patients who had undergone a non-interventional endoscopic procedure according to each data source could be determined.

RESULTS

Variceal screening among cirrhotic patients

The 'entire period' study population consisted of a total of 2741 patients diagnosed with cirrhosis between 1 January 2005 and 31 December 2016, of whom 46% (1272/2741) had undergone endoscopic screening (determined using procedure codes) by 31 December 2016. 249 (9.1%) patients died without ever being screened, with a median time to death of 1.62 years. Nine of these deaths had variceal bleeding as an underlying/contributing cause of death. The annual number of patients with a first diagnosis of cirrhosis rose steadily from 83 in 2005 to 387 in 2016. The annual proportion of all diagnoses estimated to be based on transient elastography also rose rapidly over the study period, to a high of 69% in 2014 (Supporting Information, Table S3). The annual number screened increased from 25 (in 2005) to 170 (in 2013), and then declined to 130 in 2016 (Fig. 1). The most frequently occurring endoscopic procedure code was G45.9 ('Unspecified diagnostic fibreoptic endoscopic examination of upper gastrointestinal tract'), accounting for 73% of screening records. Three hundred and thirty-two endoscoped patients died (5% with variceal bleeding as an underlying/contributing cause) before the end of follow-up.

Table 1 compares the patient characteristics between patients screened within +/- 12 months of cirrhosis diagnosis and patients not screened by 31 December 2016. There were proportionally more screened patients amongst those ever initiated on antiviral therapy, compared with never initiated (35% vs. 27%; P<0.001), and amongst patients with non-white compared with white ethnicity (43% vs. 32%; P=0.014)**.** Of the screened patients, 6.8% (63/927) had undergone

endoscopic investigation in the 6–12 month period preceding cirrhosis diagnosis, and 12.6% (117/927) within the six months preceding diagnosis. The median time interval between date of cirrhosis diagnosis and endoscopy amongst the 747 patients screened after diagnosis was 177 days (interquartile range: 77–492 days).

Over the entire study period, 1631 patients were ever initiated on IFN-containing or IFN-free antiviral therapy, of whom 813 had a start date of treatment on or subsequent to 9 June 2014 (i.e., the date sofosbuvir approved by Scottish Medicines Consortium[13]). The difference in the proportions of patients screened according to baseline history of antiviral therapy also varied between pre-IFN-free (2005-2013) and IFN-free (2014-2016) therapy eras. In the pre-IFN-free era, 54% vs 58% (treated vs. not treated at baseline) were endoscopically screened, compared with 22% vs. 31% (treated vs. not treated) in the IFN-free era (Supporting Information, Table S2).

Among the '2005-2015' study population, 37% (876/2354) were endoscoped within the 12 months preceding or following cirrhosis diagnosis date (Table 2). Multifactorial logistic regression indicated a significantly decreased odds of being screened for persons aged <40 years (OR=0.61, 95% CI: 0.48–0.77) and aged 60+ years (OR=0.67, 95% CI: 0.48–0.94) at time of diagnosis (compared with the reference age-group 40-49 years), patients with historical alcohol consumption of ≤50 units per week/not known (OR=0.75, 95% CI: 0.63–0.90) compared with >50 units/week, patients previously initiated on antiviral therapy (OR=0.70, 95% CI: 0.55–0.89), mode of cirrhosis diagnosis of 'other/NK' (OR=0.69, 95% CI: 0.52–0.90) compared with radiology, and cirrhosis diagnosis in 2014-2015 compared with 2008-2010 (OR=0.67, 95% CI: 0.52–0.86).

Sensitivity analyses. Comparable multifactorial logistic regression analyses conducted for specific subgroups as sensitivity analysis (Supporting Information, Table S4) indicated that for patients with more advanced disease (i.e., ascites) at baseline and for those patients not known to

have been diagnosed using transient elastography, the adjusted odds of screening were lower for cirrhosis diagnoses made in 2014-2015 compared with 2008-2010 (OR=0.34, 95% CI: 0.14-0.84 and OR=0.62, 95% CI:0.43-0.90, respectively).

Sixty-two percent of the '2005-2015' study population had a platelets test result around the time of cirrhosis diagnosis. There was a strong correlation (Pearson r=0.94) between year of cirrhosis diagnosis and median platelet count for these patients. The adjusted ORs of screening associated with period of diagnosis among both patient subgroups (i.e., with platelet count ≤150k/mm^3 and >150k/mm^3) tended to decline with period (Supporting Information, Table S5), but the odds of screening in the later periods are not statistically significantly lower than for the reference period, and there was no indication of a stronger reduction in the odds of screening for the >150k/mm^3 subgroup.

First admission for bleeding varices following cirrhosis diagnosis

Among the 'entire period' study population, a total of 88 cirrhotic patients had a first bleed between date of cirrhosis diagnosis and 31 December 2016. Fifty-two percent (46/88) of these patients subsequently died, prior to 31 December 2016. Twenty-two (0.8%) patients died without a first hospital admission for variceal bleeding. The two most frequent underlying causes of death codes for these 22 patients were: R99 (*other ill-defined and unspecified causes of mortality* [6/22] and X42 (*accidental poisoning by and exposure to narcotics and psychodysleptics* [5/22]).

The annual number of patients with first bleeds reached a peak of 20 in 2015, followed by a drop to 11 in 2016 (Fig. 1). Unadjusted variceal bleeding rates declined from the first (2005-2007) to the third (2011-2013) triennium of the study period (Table 3), but the Cox regression analysis indicated no evidence for differing hazard ratios for bleeding in any triennium compared with the reference period 2008-2010. A higher hazard of bleeding was associated with the presence of

ascites only (HR=2.95, 95% CI: 1.79–4.86), and there was a lower hazard of bleeding associated with achievement of SVR (HR=0.56, 95% CI: 0.32-0.97).

Validation of the endoscopic procedure codeset

Taking the data on the HCV Clinical Database to be the gold standard, 113 GRI patients underwent an endoscopic procedure in 2005-2016, of whom 107 also had a relevant procedure indicated on SMR01.

DISCUSSION

In our national-level study population of 2,741 patients with chronic HCV infection and cirrhosis, we found that despite a steep rise in the cumulative number of cirrhotic patients over the study period, the annual number of first hospital admissions for variceal bleeding increased only slightly over the same period. Although the number of endoscopically screened patients increased steadily over time (Fig. 1), the uptake of variceal screening was consistently low (34% within the 12 months preceding or following diagnosis), and there was a significant drop in the odds of screening in the IFN-free era (2014-2015) compared with the reference period, even once relevant patient characteristics and other confounders were adjusted for. This finding held up in comparable analyses of subgroups of patients deemed less likely to have mild disease (Supporting Information, Table S4).

The low odds of endoscopic screening associated with antiviral treatment (adjusted odds ratio of 0.67) – despite current recommendations to screen following cirrhosis diagnosis – is notable, and may partly reflect patients' unwillingness to undergo an invasive procedure upon achieving SVR. In addition, many patients with FibroScan® scores in the low cirrhotic range upon diagnosis may normalize sufficiently post-treatment such that the risk of bleeding becomes low enough that screening is no longer warranted, when their FibroScan readings are no longer in the cirrhotic

range and their platelet counts are >150k/mm^3 (A. Fraser, pers. comm.).

We observed a downward trend in the rate of admission with a first variceal bleed over time (Table 3); however, after adjustment for patient factors, antiviral treatment/outcome and the occurrence of other decompensation events, there was no evidence for a statistically significant drop in the hazard ratio for bleeding in either of the two most recent triennia (2011-2013, 2014-2016), compared with the reference triennium 2008-2010. Our study could not elucidate the cause of the apparent decline in bleeding rates over time, because we lacked data on primary prophylaxis administered to either screened or non-screened patients. In addition, we could not directly compare rates of first admission with bleeding varices between screened and non-screened patients, because we did not have information of what kind of primary prophylaxis (if any) had been administered to patients in each group.

Because the observed declining trend in the rate of a first variceal bleed over triennium reached a stable (low) point in 2011-2013 of 7.1/1,000 person-years, this finding might be attributed to the introduction of IFN-free therapies, which – through widespread treatment of cirrhotic patients beginning in 2014 – has been shown to be associated with a reduction in new cases of hepatic decompensation.[6] At the individual patient level, achieving an SVR was associated with a greatly reduced risk (adjusted HR of 0.56) of a first variceal bleed. However, IFN-free therapies cannot explain the low variceal bleeding rate observed prior to 2014; thus, it remains unclear whether this currently low rate is related to diagnosis of earlier stage cirrhosis, effective endoscopic screening, pharmacological prophylaxis, or other factors.

Screening rates in our cohort concur with findings of a large study using the US Veterans Health Administration database,[5] in which 34% of HCV-infected patients with cirrhosis were endoscopically screened per AASLD guidelines within the 1 year preceding or 1 year following

cirrhosis diagnosis. In our study, 34% of patients diagnosed with cirrhosis 2005-2016 had been screened within the 1 year preceding or following diagnosis.

Strengths of our study are good internal validity; high database coverage (17/18 specialist clinics) means that almost all cirrhotic patients in tertiary care were included. However, because attendance at a clinic would normally be a prerequisite for diagnosis of cirrhosis and variceal screening, our results cannot be generalised to HCV-infected persons with (largely asymptomatic) cirrhosis not attending specialist care.

The principal reason that a patient may not be referred for endoscopic screening, which our study was unable to address, is the possible substitution of non-selective beta-blockers without (invasive) endoscopy. We necessarily assumed 100% eligibility – all cirrhotic patients – for endoscopic screening, ignoring other, possibly unmeasured, clinical factors such as co-morbidities that might make a patient ineligible. As well, achievement of viral clearance through antiviral therapy may influence the likelihood of screening; we attempted to adjust for this through inclusion of a covariate for history of antiviral treatment in the logistic regression analysis, and we observed a reduced odds of screening among the subset of patients who had previously been initiated on treatment. A further factor that may underlie the drop in screening uptake in the IFN-free treatment era, which we could not measure, is a potential change in referral practice. Because of better tolerability of the new regimens, many patients are now being treated by an infectious disease specialist whereas they previously would have been referred to a gastroenterologist or hepatologist (who may be more inclined to screen for varices). However, recent changes in variceal screening guidelines[14] that recommend the use of non-invasive markers to identify patients at very low risk of developing bleeding varices are unlikely to have influenced practice across our analysis timeframe, with the possible exception of the final year of our study period. The sensitivity analysis among the patient subgroup with available platelets

counts also did not suggest increasing application of Baveno VI criteria, but was consistent with a trend in the frequency of diagnosis of less advanced disease over time. As the use of criteria based on non-invasive markers becomes more widespread to spare unnecessary endoscopies, even lower screening uptake may be observed in future, and monitoring of uptake will need to take factors such as antiviral treatment into consideration.[16,17]

The origin of the apparent downward trend in bleeding rates between 2005 and 2011-2013 is multifactorial; possible reasons include – among others – diagnosis of cirrhosis made in patients with milder disease (due to increasing use of transient elastography; Supporting Information, Table S3) in more recent years, more effective screening for varices, and slowing of decompensation due to improved clinical care,. In addition, we could only crudely adjust for severity of liver disease in the regression analysis, as we lacked data on prognostic factors such as the Child-Pugh score or the hepatic venous pressure gradient as a measure of clinically significant portal hypertension.[15] A possible influential factor (which could not be addressed in the current study) may be the changes in recommendations for pharmacological treatment as primary prophylaxis against variceal bleeding.[7] Historically propranolol was used in Scotland, but around 2008 many clinicians transitioned to carvedilol, which has superior portal haemodynamic effects in cirrhosis.

A further limitation is our assumption that all gastroesophageal endoscopic examinations were carried out for variceal screening purposes; we could not distinguish other reasons for the procedure using our linked dataset. Nineteen percent (180/927) of our cirrhotic patient pool had a date of cirrhosis diagnosis up to 12 months following endoscopic examination. For some of these patients, the clinician may have made a cirrhosis diagnosis upon viewing the endoscopy results, but this may have not been recorded in the database until much later. Finally, incomplete data on the HCV Clinical Database regarding patients' historical alcohol intake and the

occurrence of decompensation events, as well as record-linkage errors between this database and SMR01, may have lead to biased estimation of effect measures in either regression analysis.

Conclusions. Uptake of variceal screening following cirrhosis diagnosis among Scotland's chronic HCV-infected population has been historically low, and the observed decline into the era of IFN-free therapy is a potential cause for concern. This decline does not appear to be attributable to patients being diagnosed at an earlier stage of cirrhosis over the study period (i.e., possibly due to increasingly frequent use of transient elastography), as a significant drop in uptake in 2014-2016 was also observed in sensitivity analyses of subgroups of patients with ascites at baseline and patients not known to have been diagnosed using transient elastography. As HCV treatment becomes more devolved from hospital-based to community-based (primary care and other non-specialists), there is at risk that patients – often from harder to reach populations – needing variceal screening may not be identified, or be less responsive to engaging with screening. Because the annual number of first admissions for bleeding varices was relatively constant over time, despite a steep rise in new cirrhosis diagnoses, our analysis suggests that active prevention initiatives – including effective variceal screening – may have contributed to this observation, but changing diagnostic procedures over the study period resulting in diagnosis of cirrhosis at earlier, even asymptomatic, stages, could also underlie the stable numbers of annual admissions and lack of changing risk of bleeding over time. The halved risk of bleeding associated with antiviral therapy-induced viral clearance (hazard ratio of 0.56) is reassuring and counteracts the potentially negative impact of a lower screening uptake in an era in which patients with compensated cirrhosis can be safely and effectively treated.

STATEMENT OF INTERESTS

Authors' declaration of personal interests. STB reports receipt of speakers fees from Abbvie, Gilead, and advisory board fees from Abbvie, BMS, Gilead, MSD. SJH has received honoraria for presenting at meetings/conferences from Gilead. JFD reports grants and personal fees from Roche, MSD, Janssen, Gilead and Abbvie, personal fees from BMS, and grants from GSK. DJG reports personal fees from Abbvie and personal fees from Gilead and MSD. EP reports personal support from Gilead, Abbvie and BMS. NK reports participation in Advisory Boards for Gilead, Merck, Abbvie, and Janssen. PCH has received personal support from Roche, Janssen, MSD and Gilead. All other authors report no potential conflicts of interest.

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AUTHORSHIP STATEMENT

The article guarantor is SAM. Specific author contributions: study concept and design (SAM, PCH, STB, SJH); analysis and interpretation of data (SAM, STB, SJH, AJS, AF, JFD, HAI, DJG, PCH); drafting of the manuscript (SAM); critical revision of the manuscript (SAM, STB, SJH, AJS, AF, JFD, HAI, EP, NK, AB, PB, JM, DJG, PCH). All authors have approved the final version of the manuscript, including the authorship list.

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Table 1. Baseline characteristics of the cirrhotic chronic HCV-infected study population (N=2741), comparing patients who were not endoscopically screened for varices within +/- 12 months of date of cirrhosis diagnosis and those who were screened.

Variable	Not screened N (col %)	Screened N (col%)	Row %	P-value
Total	1814 (-)	927 (-)	33.8%	
Female	446 (24.6)	241 (26.0)	35.1%	0.45
Male	1386 (75.4)	686 (74.0)	33.4%	
Age at cirrhosis				<0.001
<40	394 (21.7)	145 (15.6)	26.9%	
40-49	732 (40.4)	444 (47.9)	37.8%	
50-59	506 (27.9)	256 (27.6)	33.6%	
60+	182 (10.0)	82 (8.8)	31.1%	
Ethnicity group				0.014
Non-white	93 (5.1)	70 (7.6)	42.9%	
White	1721 (94.9)	857 (92.4)	32.3%	
Risk group				0.34
Non-PWID/NK	634 (35.0)	363 (39.2)	36.4%	
PWID	1180 (65.0)	564 (60.8)	32.3%	
Alcohol use history				<0.001
>50 units/wk	636 (35.1)	416 (44.9)	39.5%	
≤50 units/wk or NK	1178 (64.9)	511 (55.1)	30.3%	
Period of cirrhosis diagnosis				<0.001
2005-2007	153 (8.4)	114 (12.3)	42.7%	
2008-2010	286 (15.8)	203 (21.9)	41.5%	
2011-2013	583 (32.1)	336 (36.2)	36.6%	
2014-2016	792 (43.7)	274 (29.6)	25.7%	
Initiated on antiviral therapy at baseline				<0.01
No	1488 (82.0)	806 (86.9)	35.1%	
Yes	326 (18.0)	121 (13.1)	27.1%	
Ascites at baseline				0.021
No	1656 (91.3)	820 (88.5)	33.1%	
Yes	158 (8.7)	107 (11.5)	40.4%	
Encephalopathy at baseline				<0.001
No	1673 (92.2)	911 (98.3)	35.3%	
Yes	141 (7.8)	16 (1.7)	10.2%	
Mode of cirrhosis diagnosis				<0.001
Radiology†	1377 (75.9)	762 (82.2)	35.6%	
Clinical exam.	205 (11.3)	62 (6.7)	23.2%	
Other/NK†	232 (12.8)	103 (11.1)	30.7%	

Note. PWID=people who inject drugs; NK=not known. *P*-values from chi-squared test comparing frequency distributions between screened and not screened patients. †Radiology includes ultrasound and Fibroscan. Other/NK includes biopsy (25%), LFTs and platelets (20%), hyaluronic acid (39%), endoscopy (11%), and NK (5%).

Table 2. Results of logistic regression analysis of the odds of variceal screening within +/- 12 months of cirrhosis diagnosis; the study population is defined as patients with date of cirrhosis diagnosis between 1 January 2005 and 31 December 2015 (N=2354).

		Unadjusted		Adjusted	
Covariate	n	OR	(95% CI)	OR	(95% CI)
(All)	876	-		-	
Male	650	Ref.		Ref	
Female	226	1.07	(0.88-1.29)	1.09	(0.90-1.34)
Age					
<40	143	0.65	(0.51-0.82)	0.61	(0.48-0.77)
40-49	421	Ref.		Ref.	
50-59	240	0.83	(0.68-1.01)	0.82	(0.67-1.01)
60+	72	0.70	(0.51-0.95)	0.67	(0.48-0.94)
Ethnicity group					
Non-white	65	1.36	(0.97-1.91)	1.38	(0.96-1.99)
White	811	Ref.		Ref.	
Risk group					
Non-PWID/NK	341	1.13	(0.95-1.35)	1.19	(0.98-1.45)
PWID	535	Ref.		Ref.	
Alcohol use history					
>50 units/wk	390	Ref.		Ref.	
≤50 units/wk or NK	486	0.73	(0.62-0.87)	0.75	(0.63-0.90)
Period of cirrhosis diagnosis					
2005-2007	114	1.05	(0.78-1.42)	1.06	(0.78-1.46)
2008-2010	203	Ref.		Ref.	
2011-2013	336	0.81	(0.65-1.02)	0.80	(0.63-1.01)
2014-2015	223	0.69	(0.54-0.88)	0.67	(0.52-0.86)
Initiated on antiviral therapy (at baseline)					
No	760	Ref.		Ref.	
Yes	116	0.68	(0.54-0.86)	0.70	(0.55-0.89)
Ascites					
No	820	Ref.		Ref.	
Yes	107	1.38	(1.04-1.82)	1.27	(0.92-1.75)
Encephalopathy					
No	911	Ref.	Ref.		
Yes	16	0.57	(0.30-1.08)	0.57	(0.28-1.19)
Mode of cirrhosis diagnosis					
Radiology†	718	Ref.		Ref.	
Clinical exam.	57	0.95	(0.67-1.33)	0.88	(0.58-1.34)
Other/NK†	101	0.78	(0.60-1.01)	0.69	(0.52-0.90)

Note. PWID=people who inject drugs; NK=not known.

†Radiology includes ultrasound and Fibroscan. Other/NK includes biopsy, LFTs and platelets, hyaluronic acid, endoscopy, and NK.

Table 3. Results of Cox regression analysis to estimate the unadjusted and adjusted hazard ratios (HR) of variceal bleeding associated with period;the study population is defined as all patients with date of cirrhosis diagnosis between 1 January 2005 and 31 December 2016 (N=2740).

Covariate	n	Follow-up (yrs)	Rate per 1000 p-yrs	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
(All)	88	9406	9.4	-	-
Male	67	6988	9.6	Ref.	-
Female	21	2417	8.7	0.90 (0.55-1.47)	-
Age					
<40	15	1298	11.6	1.24 (0.67-2.28)	-
40-59	34	3715	9.2	Ref.	-
50-59	24	3080	7.8	0.89 (0.52-1.50)	-
60+	15	1312	11.4	1.36 (0.74-2.52)	-
Period					
2005-2007	7	341	20.6	1.81 (0.71-4.60)	1.64 (0.64-4.22)
2008-2010	13	1086	12.0	Ref.	Ref.
2011-2013	20	2815	7.1	0.64 (0.32-1.29)	0.76 (0.37-1.55)
2014-2016	48	5164	9.3	0.87 (0.47-1.63)	1.25 (0.65-2.42)
Alcohol use history					
>50 units/wk	44	3659	12.0	Ref.	Ref.
≤50 units/wk or NK	44	5746	7.7	0.63 (0.41-0.95)	0.76 (0.50-1.18)
Mode of cirrhosis diagnosis					
Radiology†	63	7005	9.0	Ref.	Ref.
Clinical exam.	11	688	16.0	1.85 (0.97-3.51)	1.00 (0.50-1.99)
Other/NK†	14	1713	8.2	1.02 (0.57-1.84)	1.07 (0.57-1.98)
Antiviral therapy/outcome					
Never treated	60	5190	11.6	1.06 (0.55-2.05)	
Treated/non-SVR	11	1077	10.2	Ref.	Ref.
Treated/SVR	17	3138	5.4	0.54 (0.25-1.16)	0.56 (0.32-0.97)
Ascites					
No	59	8157	7.2	Ref.	Ref.
Yes	29	1249	23.2	3.33 (2.13-5.20)	2.95 (1.79-4.86)
Encephalopahy					
No	82	9008	9.1	Ref.	-
Yes	6	398	15.1	1.65 (0.72-3.78)	-

Note. Age, ascites, encephalopathy, antiviral treatment outcome, and antiviral therapy/outcome all defined as time-dependent covariates.

†Radiology includes ultrasound and Fibroscan. Other/NK includes biopsy, LFTs and platelets, hyaluronic acid, endoscopy, and NK.

*Reference category for adjusted analysis is aggregate of Never treated and Treated/non-SVR categories, as univariate analysis indicated a HR near 1.0.

FIGURE LEGEND

Fig. 1. Upper panel: annual number of patients endoscopically screened among population of chronic HCV-infected patients diagnosed with cirrhosis between 1 January 2005 and 31 December 2016 (screened within 12 months prior to or at any time after cirrhosis diagnosis). This panel also shows the annual number of first admissions for bleeding varices following cirrhosis diagnosis in the same study population. Lower panel: annual proportion of newly diagnosed cirrhotic patients screened within 12 months prior to or following diagnosis date, with 95% confidence band.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	√ (*a*) Indicate the study's design with a commonly used term in the title or the abstract
		√ (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	√ Explain the scientific background and rationale for the investigation being reported
Objectives	3	√ State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	√ Present key elements of study design early in the paper
Setting	5	√ Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	√ (*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	√ Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	√ For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	√ Describe any efforts to address potential sources of bias
Study size	10	√ Explain how the study size was arrived at
Quantitative variables	11	√ Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	√ (*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		√ (*e*) Describe any sensitivity analyses
Results		
Participants	13*	√ (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	√ (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	√ Report numbers of outcome events or summary measures over time
Main results	16	√ (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		√ (*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	√ Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	√ Summarise key results with reference to study objectives
Limitations	19	√ Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias

Interpretation	20	√ Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	√ Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based